Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: *Noninvasive Testing for Coronary Artery Disease*

Draft review available for public comment from August 5, 2015 to September 2, 2015.

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Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	Introduction	Intro is appropriate and introduces the problem. It would be helpful to more clearly describe the difference between functional and anatomic tests earlier in the document to ensure that all are focused on the clear differences.	Thank you for your comments. The initial description of anatomic and functional tests is on page 2 of the full report. We felt it was most logical after describing the anatomic and physiologic changes that occur with CAD and have not made any changes.
Peer Reviewer 2	Introduction	Appropriate	Thank you.
TEP 2	Introduction	There are a number of problematic details in the Introduction as listed below: p. 2, line 36 - Diagnosis of CAD: Overview - this section appears to refer exclusively to ED patients. Patients are also seen initially in outpatient clinics with stable angina. The workup is completely different and may consist of a history and an ECG, followed by some noninvasive testing. This part needs to be rewritten with this in mind.	Revisions have been made to the text for this section as well as in the Executive Summary.
TEP 2	Introduction	p. 2, line 45 - "discharged"? Again, this refers only to patients seen in the ED. Many of these patients are seen in outpatient clinics, not in the ED, so this term is not correct. This is relevant to comment 1 above.	Revisions have been made to the text for this section as well as in the Executive Summary
TEP 2	Introduction	p 5, line 19 - stress echocardiography is qualitative and not semi-quantitative p 5, lines 22-24 - in general, SPECT and stress echo offer overall similar accuracy but SPECT has a higher sensitivity and echo a higher specificity p 5, line 35 - infarction, not infraction p 5, line 38 - the cost of a stress MRI is no different and in many cases is lower than stress SPECT. This is a common misconception. Since cost was not an explicit goal of this document and was not examined carefully, any mention of relative costs of noninvasive studies should be removed.	The typographical error has been corrected to read “infarction”. “Semi-quantitative” has been removed to avoid misunderstanding in this text;, however, team clinicians indicate that calculations of specific factors are possible with both echocardiography and nuclear testing. Although cost is not explicitly evaluated in the systematic review, information is provided for general context and felt to be relevant. Based on input from team clinicians, cardiac MRI (CMR) is generally more costly than nuclear imaging when one considers costs of equipment, infrastructure, etc. Certainly, equipment costs for MRI are higher and CMR is not available in clinic offices. We revised the text to specify the ”high cost of equipment.”

Commentator & Affiliation	Section	Comment	Response
TEP 2	Introduction	p 5, lines 39-40 - this sentence "An additional concern...." should be removed. I reviewed reference 27 and there is no discussion about downstream testing and unintended findings. The point of the reference was for the need for outcome studies of which there are few with cardiac MRI.	The reviewer is correct in that the overall point of the article is that research is needed to show whether diagnostic imaging plays a role in improved patient outcomes. However, some of the unknowns regarding CMR in relation to other tests such as downstream testing, cost-effectiveness, and availability are also described. Edits have been made to the sentence to better reflect the referenced source.
TEP 2	Introduction	p 5, line 58 - adoption is not low. It is quite variable amongst institutions and states, primarily due to issues with insurance coverage, not with clinical utility or interest.	We have reworded this to indicate that adoption is variable across settings, institutions, and states.
TEP 2	Introduction	p 6, last paragraph - I am not sure that CACS really belongs in this document as it is used for screening purposes not for diagnosis of obstructive CAD and as such is really not comparable to any of the other tests that are discussed. I would recommend removing any discussion of CACS from the document.	We agree that CACS does not provide information on obstructive CAD and may not be considered a diagnostic method as it measures amount of calcium present, not obstruction. While CACS is generally considered a screening tool, some TEP members felt that it should be included and based on initial preliminary search, there appeared to be studies describing its use in symptomatic patients, suggesting that it may be used outside of screening of asymptomatic persons.
TEP 2	Introduction	p. 7, Exercise ECG, Advantages - what is meant by "prognostic 3-vessel disease". This is some kind of typo.	Wording has been changed to reflect the idea that exercise ECG is unlikely to miss significant disease such as multivessel or obstructive left main CAD.
TEP 2	Introduction	p. 8, Stress PET - General use - it is used clinically where it is available. Rather than "Rarely used clinically" it should read "Less clinically available". In Disadvantages - "Data to support PET is limited". There are growing outcomes data sets with PET. This statement should be removed.	This has been reworded to “less clinically available” and the statement regarding support for PET has been removed.
TEP 2	Introduction	p. 9, stress CMR, General Use - again, as for PET, rather than "Rarely used clinically" it should read "Less clinically available". Would remove "and can assess some cardiac indices (stroke volume)" as this adds little. Would add to typically pharmacologic - "generally vasodilator oerfysuib	All but one of these edits have been made to the table; team clinicians reaffirmed that CMR is more costly than most other noninvasive tests and probably more costly than nuclear testing when one

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		stress is much more commonly performed than dobutamine functional stress". Under Advantages = "spatial" not spacial. Would remove "Imaging of arterial wall and plaque" as this is irrelevant to this topic. Would also remove "flow mapping with contrast" as this is repetitive of the next item. Under Disadvantages - Would remove "Costly", as discussed above and would remove "Long procedure time". A stress CMR can be done in 35-40 minutes, whereas it takes 4 hours to do a rest and stress SPECT exam! Would add "Complex exam that requires specialized training". Under Diagnostic Threshold... Abnormal - Would change to "Vasodilator - any perfusion abnormality and/or infarct on late gadolinium enhancement. Dobutamine - any or worsening new wall motion abnormality."	considers costs of equipment, infrastructure, etc.
TEP 2	Introduction	p. 10, CTA - EBCT is no longer used. Any mention of it in the document should be removed. Remove the bullet point "In EBCT or MDCT...." as this only refers to EBCT. Under Diagnostic Threshold - Abnormal is not Any Luminal Regularities. It is a stenosis>50%.	We understand that EBCT is no longer used; however, reference to it was included in the event that older CACS studies using EBCT would meet inclusion criteria. The comment that >50% stenosis rather than any luminal irregularities is used for CT is correct when trying to understand cause of chest pain. Luminal irregularities are however still important for establishing need for secondary prevention strategies for preventing disease advancement. This clarification has been added to the table.
TEP 2	Introduction	p.11 - again, CACS should be removed since it is a screening test quite different from the others discussed.	Some TEP members felt that it should be included and based on our initial preliminary search, there appeared to be studies describing its use in symptomatic patients, suggesting that it may be used outside of screening of asymptomatic persons.
TEP 2	Introduction	p.2(?), p 56/342 in PDF - the #'s for CTA are inflated and based on one meta-analysis of low-dose studies. The specificity listed is much higher than that of multi-center studies (ACCURACY, etc.) Another useful meta-analysis might be Paech DC et al BMC CV Disorders p. 7(?), p 61/342 , line 32 - remove extra words "PCI reduces the incidence of angina"	The section on accuracy is provided for context only and not based on comprehensive systematic review. The data presented in Table 3 are from a systematic review of studies of CT with low dose radiation. Data from the Paech review (rated as being moderately high

Commentator & Affiliation	Section	Comment	Response
			risk of bias) has been added for additional context; radiation dose was not specified in the Paech review.
TEP 2	Introduction	p. 7(?), p 61/342 , line 35 - CABG involves grafting of arteries (linternal mammary) and/or veins (saphenous). Remove "local or transplanted vein".	Revision made. Thank you.
TEP 2	Introduction	p 297/342, Appendix H5 - a more updated meta-analysis than the Nandalur reference is Hamon N, J Cardiovasc Magn Reson 2010	The Hamon publication focuses on perfusion MRI, which was not within the scope of this review. The intent of the contextual section on test accuracy is to provide an overview of accuracy in populations of interest for the comparators in the review; it was not intended to be comprehensive.

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TEP 3	Introduction	There is some confusion about whether this paper addresses stable outpatients ("stable, symptomatic patients who have no known history of CAD", p. 6) or also includes acutely symptomatic patients in the ED, i.e., acute coronary syndrome or ACS ("This is more frequently done in patients who present to the emergency room with typical symptoms", p. 12). Similarly Fig. A is ambiguous on this point at the level of entry into the algorithm.	We have added clarification throughout the report with respect to exclusion of those with ACS. The focus of the report is on stable patients. Per our protocol patients with definite acute coronary syndrome (ACS), Non-ST-Elevation Acute Coronary Syndromes (NSTE-ACS), NSTEMI, and STEMI were excluded, as were those with unstable angina with elevated serum cardiac biomarkers, ECG changes, etc. This is also reflected in the PICOTS table. We have reviewed included studies to confirm that such patients were excluded or did not comprise >20% of study populations based on data reported in the included studies. Team clinicians agreed that with these exclusions, the population was likely at the “high” end of the intermediate range versus patients who were high risk presenting with ACS. Team clinicians also confirmed that there may be substantial variability across clinical settings and regions. The range of patients who present to the ED may include those with stable symptoms and low probability of CAD and those patients with intermediate pretest probability as well as those with ACS requiring immediate care (e.g. those having an MI at presentation). Figure 1 is intended to provide a general algorithm for patient evaluation, regardless of entry point. The text discussion on page 4 is also intended to provide a general overview of possible options at various pretest risk levels (including high); The protocol and PICOTS provide information on exclusion of the definite “high” risk group (i.e., those with ACS).

Commentator & Affiliation	Section	Comment	Response
TEP 4	Introduction	Yes to all.	Thank you.
TEP 5	Introduction	I have no specific thoughts on the Introduction section proper, but seeing how there is no separate section to critique the abstract, I will offer one thought on the abstract: it would be good if the authors found a way to briefly present their definitions for the various levels of "strength of evidence" already in the abstract. This would make the rest of the abstract so much easier to understand.	A sentence has been added to the abstract. Thank you.
TEP 6	Introduction	The introduction is well-written and appropriately describes the relevant background for both a reader very familiar with the subject area as well as someone who may not specialize in the field.	Thank you.
TEP 6	Introduction	The overview of pre-test probability is very informative as it relates to the risk assessment definitions used in the studies that are captured in the evidence review. One questions arises as to why the Framingham Risk Score is not included as another risk estimation used as it appears in studies that compare CCTA verses SPECT (p60) and included in Appendix D as a data extraction element (p D-1, line 38).	Where risk scores were available, regardless of how they were derived, the data were included in the description of studies in the report and in the appendices. Many studies did not provide detail regarding how pretest risk was assessed. This may partially be a reflection of the fact that standardized tools and algorithms are generally not used to assess pretest probability. The review team spent substantial time considering ways to standardize presentation of reported risk scores. Even trials that used the same method used different thresholds to determine low, intermediate, etc. Some used multiple methods to determine pretest risk. Clinical features were variably reported across studies and assumptions regarding typicality of chest pain, etc. were not considered appropriate; this led to variable results for pretest risk, which sometimes were very different than the author-defined pretest risk.

Commentator & Affiliation	Section	Comment	Response
TEP 6	Introduction	The overview of the non-invasive tests included in the report particularly the sensitivity and specificity data for populations.	Thank you.
TEP 6	Introduction	The table on radiation exposure is also an important piece of background. The one comment that I have on that table is the challenge in the ranges and in the interpretation of them. For example, for CCTA, there are 4 different sources of estimates of radiation exposure, thus the range really moves from 0.5-50 without a great explanation as to why or when someone may receive only 0.5mSv of radiation as compared to when something like 50mSv would be received.	Edits have been made to the table. Radiation exposure is influenced by a number of factors, including prospective gating, multidetector rows, better processing, and of course patient body morphometrics that influence energy. Edits to the text have been added to this effect. (The 0.5-1 mSv would likely be a patient with a prospectively gated study; 5-15 mSv would be a retrospectively gated study and may include both non-contrast and contrast study +/- additional structures in the chest. The Einstein paper, which references up to 50 (and even 100 mSv), is reporting cardiac CT scans that are not used for the purposes of identification of coronary artery disease (but rather were used as part of a pre-TAVR protocol that involves extensive imaging of the chest, abdomen, and pelvis both with and without contrast). The highest dose reported in Einstein that is applicable to our population is 30 mSv in a helical CT without tube modifications. We have changed the range to 0.5-30 mSv. This is still a broad range, but represents many different techniques (prospective/retrospective capture) with variations on contrast use, etc.
TEP 6	Introduction	There is quite a bit of space devoted to medical therapy and the medical interventions for CAD in detail. However, the focus of the report rests on noninvasive testing. While, some background on medical therapy is helpful, perhaps this could be streamlined (even perhaps moving such a table as Table 5, p 6) to an appendix.	Thank you for your comments. To serve a general audience, we have kept the information in the introduction.

Commentator & Affiliation	Section	Comment	Response
TEP 7	Introduction	The introduction is generally quite lucid. The authors posit that establishing performance characteristics (e.g., sensitivity and specifity) are insufficient because unnamed authorities feel that relationship to outcomes is more relevant. This is certainly true but standard performance metrics themselves are somewhat irrelevant. They are calculated using arbitrary reference standards (e.g., 50% or 70% stenosis of a coronary artery) when the risk of adverse events bears a continuous relationship with degree of obstruction. There is no clearly definable threshold of risk. Moreover, the reliability of the degree of stenosis has been shown to be relatively low (IRR ~0.7), likely for the reasons detailed in the report (page). Because these tests yield not only diagnositic but also prognostic information, assessment of post-test probabilities, as the authors of this report suggest, would be very useful. As they also point out, because assessment of pre-test probability is difficult, assessment of incremental change in likelihood of events would be also be difficult but certainly desirable.	Thank you for your comments
TEP 7	Introduction	In addition, we know lesions most likely to precipitate ischemic events are not necessarily those that are most likely to be detected by diagnostic tests, particularly anatomic ones.	Thank you for your comments.
TEP 8	Introduction	No comments.	
Peer Reviewer 1	Methods	A particular strength is that the outcomes are all clinical outcomes, rather than just diagnostic accuracy. Inclusion and exclusion criteria are appropriate. Lit search and statistical methods are appropriate.	Thank you for your comments.
Peer Reviewer 1	Methods	However it would be helpful to include testing vs no testing in low risk groups.	No studies making a comparison to no testing in low risk groups was identified. This is listed as a gap in the current evidence.
Peer Reviewer 2	Methods	Analyses was performed in subgroups of patients stratified by different pre-test risks of CAD as defined by the authors of included studies. There is insufficient evidence from the included studies to suggest that any testing technology is superior to the others in terms of effectiveness or harms. No recommendations about the most optimal technology to use in the clinical setting can be drawn from available data.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 2	Methods	Comments This is well-written manuscript and it aimed to address an important clinical question. The population, testing technologies and outcomes were clearly defined. The search was quite exhaustive. Multiple databases were used. Follow-up reviews of relevant articles in the reference lists were performed. Unpublished studies were also assessed. The quality of the studies and strength of evidence were evaluated and accounted for in data synthesis.	Thank you.
Peer Reviewer 2	Methods	The authors used appropriate statistical methods to synthesize the data. Although they also planned to elucidate the relative effectiveness among different technologies using network meta-analysis and to test publication biases using statistical analysis, it was not performed due to the small number of studies that met the inclusion criteria.	Thank you.
TEP 2	Methods	The methods are reasonable, but as above, I would have considered including patients with known CAD as well as those with suspected CAD. Splitting the studies into level of risk is somewhat artificial as many studies don't set out to define the level of risk they are planning on testing, so doing it post-hoc may be tricky. The definitions and outcome measures used are appropriate. The inclusion and exclusion criteria listed are quite complete. The quality assessment methods are excellent.	While there may be more literature in patient s with known CAD, the intent of this review was to focus on those without known CAD as this is perhaps an area of greater controversy and less is known about testing in this group.
TEP 2	Methods	p. 15(?), 69/342 - again Calcium scoring should be removed.	While CACS is generally considered a screening tool, some TEP members felt that it should be included and based on initial preliminary search, there appeared to be studies describing its use in symptomatic patients, suggesting that it may be used outside of screening of asymptomatic persons.
TEP 3	Methods	OK	Thank you.
TEP 4	Methods	Yes to all.	Thank you.
TEP 5	Methods	In my opinion, the authors have chosen well (and logically) and documented well their search strategies as well as the inclusion and exclusion criteria for comparative studies to be considered.	Thank you.
TEP 5	Methods	The meta-analytic methods used, especially the methods chosen to account for inhomogeneity between different studies included into 1 analysis) in the data synthesis were very appropriate, to the best of my knowledge of these methods.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP 6	Methods	The inclusion and exclusion criteria are crisply stated and the table is incredibly explanatory. The special populations and circumstances of interest were appropriate and well articulated (p 14 Inclusion column). They make clinical sense for special attention. The inclusion of socioeconomic factors is an important one, but was not descriptive enough in my opinion to really explain the importance. Perhaps something, even a phrase, that describes socioeconomic factors may influence the types of tests available/offered. I think this is the point that is trying to be conveyed.	To the extent that socioeconomic factors were described and evaluated, they were included in our evaluation. Some additional language in the research gaps suggesting that these factors are not well reported was included.
TEP 6	Methods	My major comment/recommendation is that the data synthesis section of the methods could be enhanced. After reviewing the tables and figures in the results, it would be helpful if there was more information related to meta-analyses. When a meta-analysis is performed or not needs greater explanation. There is more explanation in the executive summary than there is in the methods section. For example a matrix of the pre-test probability category, and number of studies in each comparator group would be helpful to know when a meta-analysis was performed. It also is less clear to me as a non-statistician why a risk difference estimate was used and the meaning of the heterogeneity statistic. Further description of this may be helpful to the reader.	Thank you for your comments. At the beginning of the results section, a table has been added to give an overview of tests compared; the table indicates which pretest risk categories were evaluated. Risk difference (RD) provides an absolute measure for randomized controlled trial data. The absolute approach is helpful for decision making from the perspective of knowing which test has more cases per 100 (or 1000) of a clinical outcome (e.g., myocardial infarction than the other (after patients have gone through the decision/treatment pathway). The RD helps provide information on the difference in the number of people with a given outcome identified with each test. This additional information has been added to the methods. The presence of statistical heterogeneity among the studies was assessed by using the standard Cochran's chi-square test, and the magnitude of heterogeneity by using the I^2 statistic(See the methods section in the full report.) This statistical test describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). (Statement has been added to methods)

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TEP 7	Methods	Yes. Really well done, especially the differentiation by pre-test risk groups and by site of testing.	Thank you for your comments.
TEP 8	Methods	The authors reviewed over 17,000 citations and only found 45 which meet pre-specified criteria. The reasons for the significantly small number of studies should be discussed. Important conclusions deserve highlighting, including the downstream effect of testing, specifically the increased rate of invasive angiograms with coronary computed tomography angiography, CCTA.	Possible reasons for the paucity of literature are offered in the discussion section of the full report.
TEP 8	Methods	Radiation exposure is rarely reported but can be calculated in clinical and has been assessed in subsequent targeted studies.	We reported information on radiation as provided in included studies.
Peer Reviewer 1	Results	The study characteristics appear to be as clearly defined as possible, however. a major limitation is that the level of pretest risk is often not clearly defined, which makes the results difficult to generalize	Thank you. Pretest risk was reported as defined by authors of included studies; unfortunately, this was not consistently defined or in some cases not reported.
Peer Reviewer 1	Results	One important issue is the difference between patients seen in the ED vs those seen in the outpatient setting. Although the authors acknowledge in the discussion that these are two separate groups of patients, there does not appear to be any attempt to do any separate analyses of these groups of patients. i think this would be one thing that could strengthen this report: at least an attempt to do some separate analyses of patients seen in the ED vs those in the outpatient clinical setting.	No pooled analyses combined patients from ED and outpatient settings. Results tables and the report text note if the population was from ED or outpatient setting. It is unclear what additional analyses would be fruitful.
Peer Reviewer 2	Results	The results were voluminous and relatively dense.	Yes. We made the presentation of the complex findings as concise as possible while not leaving out details necessary for accurate understanding.
TEP 2	Results	The amount of detail in the results is somewhat overwhelming, but to be expected for this kind of document. The meta-analysis graphs are problematic in that they don't list the tests being compared on the graph so one has to guess which side the confidence intervals fall on. The studies included and excluded are generally appropriate for the definitions used. Again, known CAD might have been something to examine as well.	Meta-analysis plots have been labeled. The intent of the review was to evaluate studies in patients without known CAD.
TEP 2	Results	p. 61, 115/342, lines 39-45 - PET is listed but the study compared CTA to SPECT.	This has been corrected.

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TEP 3	Results	See above comment in setting of this statement, "Available data from studies conducted in EDs were primarily for the index ED visit and is noted. Outcomes such as MI at the time of the ED index visit were considered to reflect diagnosis of MI at that time. Where available, data on longer term followup is presented." This statement clearly reflects a focus on the ACR group as by definition patients in the ED are suffering from suspected ACR rather than chronic stable angina. For example in the Low Risk category, the two foci mentioned (CCTA vs. usual care and SPECT vs. exercise ECG) are explicitly directed at two different and mutually exclusive patient populations (ACS vs. chronic stable angina). At a minimum the paper should be reorganized to address ACS and chronic stable angina separately rather than mixed together in Low, Intermediate, and High risk groups as presently. The same goes for all studies referencing ED patients which I won't go on to identify individually in the interests of conciseness.	The response below assumes “ACR:” actually represents “ACS”. Our review included patients enrolled through emergency rooms. We verified that included studies explicitly either excluded patients with acute coronary syndrome (ACS) prior to their enrollment *or* that the population did not comprise >20% of patients with ACS based on data reported in the included studies. One subanalysis of high risk patients from one study did contain >20% of patients with ACS (myocardial infarction) and was deleted from the results. All others met the criteria. Team clinicians agreed that with these exclusions, the populations in these studies were likely at the “high” end of the intermediate range versus patients who were high risk presenting with ACS who were unstable and would follow a different diagnostic and clinical decision making pathway. Furthermore, while some emergency departments may primarily see high risk patients with ACS, others may not. There is substantial variability across ED settings for regions across the United States, and patients from all risk levels (low to high) may present to the ED. The emergency department sees patients with a variety of causes of chest pain, many of which can mimic angina due to coronary artery disease. In patients with intermediate or high risk of occlusive coronary artery disease, the physician may elect to perform stress testing for diagnostic purposes. A negative stress test would provoke further evaluation for other etiologies of the chest pain. A positive stress test would provoke appropriate, guideline-directed management of coronary artery disease.

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TEP 4	Results	The Results section is very densely detailed and could, I believe, benefit from an additional tabular view (see high level example included as an attachment to this review) that helps the reader summarize the findings of the comparisons of subgroups of diagnostic methods.	Thank you for your suggestion. An overview table has been added to both the ES and the full report.
TEP 5	Results	The amount of detail presented in the results section is extensive, but not excessive, and commensurate with the complexity of the data involved and the analyses performed.	Thank you.
TEP 5	Results	I think that the characteristics, especially strengths and shortcomings, of the various studies that were included are well described. They authors have formulated the results and key messages of their analyses well and appropriately.	Thank you.
TEP 5	Results	I could not detect any bias in the study selection, data analysis or results reporting.	Thank you.
TEP 6	Results	The amount of detail presented in the results section is very appropriate. The organization of the summary key points followed by the details on the comparisons and tables makes the data more digestible. The data is presented in different ways that makes it easier for individuals that prefer different types of presentations of data to follow. The Tables and text are clear.	Thank you.
TEP 6	Results	The figures were more difficult to discern. It may be helpful to provide a label as to what the result leaning is on either side of zero. It also may be helpful to either expand in the methods or add footnotes as to the meaning of the risk difference and heterogeneity statistic.	Meta-analysis plots have been labeled. Additional text has been added to the methods section.
TEP 7	Results	The results are thorough and well presented. Given their volume, however, it would be nice to add one table that lists those findings that were of moderate to high strength of evidence. It would also be useful to include the respective in incidence of events so that the reader might be able to judge clinical importance. The difference in likelihood of ICD following SPECT or CCTA appears to be about 13% which is clearly clinically significant whereas the finding that that ICA was significantly (1%) more common in the CCTA group than the functional testing group by 90 days may or may not be meaningful even though it is based on high strength of evidence.	The results tables provide the percent of those in each group who experienced the outcome as well as the risk difference. Abbreviated summary tables have been added to the executive summary.

Commentator & Affiliation	Section	Comment	Response
TEP 8	Results	Important findings of no statistically significant difference in hard endpoints of death or nonfatal MI outcomes between tests is clear elucidated (p e17) but would be very important to highlight, expand upon and include in the abstract. The event rate is extremely low in this population without known CAD in the outpatient setting. The dissemination of this information alone may inform clinicians in their decision making and ultimately to help to change practice.	Thank you for your comments; nformation regarding the low frequency of all-cause mortality and myocardial infarction has also been added to the abstract and conclusions section.
Peer Reviewer 1	Discussion/ Conclusion	The major findings are that there do not appear to be any differences among the tests although the absolute numbers of many of the clinical outcomes are low, which limits the ability to show differences.	Thank you.
Peer Reviewer 1	Discussion/ Conclusion	they also acknowledge the major limitation of the challenges of appropriately defining pretest risk . a range of 10-90% is broad and pretest risk is defined differently in different populations.	Thank you.
Peer Reviewer 1	Discussion/ Conclusion	A final challenge is that the important clinical question of whether to do any test in a low risk person (given that tests are much more likely to lead to false positives and additional procedures that are unlikely to be necessary) is not addressed and it is a very important question in clinical practice.	We identified no studies evaluating testing versus no testing that met our inclusion criteria. Additional discussion of this has been added to the section on gaps in evidence and needs for future research.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 2	Discussion/ Conclusion	It makes clinical sense to stratify the analysis by pre-test risks of CAD. But only the pre-test risks reported by authors of the studies were used for stratification. Since different studies used different risk calculation scores, some studies would be misclassified if the same risk calculation score were used across the board. A sensitivity analysis could be useful to examine how much difference would it make should some of the "borderline" studies be put into a different group. If it turns out the results were much different, then it would be necessary to settle on one calculation score and contact the authors of the "borderline" studies to redo the analysis using that calculation score.	The review team spent substantial time considering ways of standardizing the findings on pre-test risks. Even trials that used the same method used different thresholds to determine low, intermediate, etc. Some used multiple methods to determine pretest risk. Clinical features were variably reported across studies and assumptions regarding typicality of chest pain, etc. were not considered appropriate and led to variable results for pretest risk, which sometimes were very different than the author-defined pretest risk. To the extent information was available in individual studies (e.g., thrombolysis in myocardial infarction [TIMI] score/other), it is reported in tables and additional information is in the appendices. Many studies did not provide detail regarding how pretest risk was assessed. This may partially be a reflection of the fact that standardized tools and algorithms are generally not used to assess pretest probability
Peer Reviewer 2	Discussion/ Conclusion	Areas that warrant future investigations were clearly discussed.	Thank you.
TEP 2	Discussion/ Conclusion	The discussion is quite reasonable and does a good job pointing out the paucity of outcome data with noninvasive testing in general. In addition, with optimal medical therapy in 2015, the event rates are quite low, making it quite difficult to show meaningful differences in outcomes with diagnostic testing without enrolling thousands of patients in studies. The implications are clearly stated and the limitations are as well. The research gaps and recommendations section is thoughtful and complete. The need to have a no-testing arm in future trials is discussed.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP 3	Discussion/ Conclusion	Increased invasive treatment (PCI or CABG) is harm in itself if not associated with demonstrable clinical benefit as these entail real, known risks (unlike radiation in which the risks are theoretical and not known).	Thank you for your comments. A statement regarding potential harms of invasive treatments in the absence of clinical benefit has been added to the section on implications for clinical decision making. Included studies did not provide data linking use of PCI or CABG to clinical outcomes; this was beyond the scope of this review.
TEP 3	Discussion/ Conclusion	As a new test, CCTA studies may be more restricted to specialty centers and the results may be less easily extended to all sites than more traditional modalities where presumably the expertise is more widespread. In this light, I don't see a lot of emphasis on multicenter to single center trials. For the reasons mentioned above, single center trials may tend to favor newer tests which may have a lower likelihood of providing similar results when extended beyond specialty centers.	Thank you for your comments. Text regarding the potential differences between multisite and single site trials has been added to the applicability section. Six RCTs evaluating CCTA were multicenter studies, and 5 were single center sites. Assessing discernable patterns between the multicenter and single center site studies is a challenge given the heterogeneity across studies with regard to pretest risk and other factors, including varied definitions of usual care.
TEP 4	Discussion/ Conclusion	Yes to the first 3 questions. With respect to the fourth/final question, I believe that some specific recommendations about standardizing design and evaluation methods in future studies as "lessons learned" would be additionally helpful to researchers. This could include strengths and weaknesses of specific methods used in the past. Perhaps this could be better handled in an additional follow on qualitative analysis of the issues identified.	The section on evidence gaps and future research recommendations has been revised.
TEP 5	Discussion/ Conclusion	The discussion section is written very well and without bias. The authors have candidly described the limitations of their review and analyses.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP 5	Discussion/ Conclusion	I am particularly pleased with how the authors have related and integrated their findings to the existing recommendations in the 2012 Stable Ischemic Heart Disease Clinical Guidelines and their 2014 update.	Thank you.
TEP 5	Discussion/ Conclusion	It is somewhat unfortunate but not unexpected that all that extensive work did not allow specific recommendations for clinical practice that are immediately pertinent. For this reason, the well-reasoned "Future Directions for Research" section is particularly pertinent, and the AHRQ would of course in a particularly good position to facilitate and coordinate such research efforts.	Thank you.
TEP 6	Discussion/ Conclusion	The implications of the major findings are clear. The Discussion and Conclusion serve to really put the findings in context. The limitations and research gaps were particularly helpful both for natural limits to the process as well as highlighting the research that could be informative for the future. The research gaps and recommendations could be more crisply stated and phrased to identify a research question.	The section on evidence gaps and future research recommendations has been revised.
TEP 6	Discussion/ Conclusion	One of the research gaps and recommendations relates to a lack of standardized approach to determining pre-test risk across studies. I actually think this is more of a limitation to the evidence review process. If there is a recommendation to standardize this, I think it requires a greater emphasis on research that further refines a solid approach to risk assessment.	Thank you for your comments
TEP 7	Discussion/ Conclusion	Generally outstanding. I would propose that the conclusions more strongly recommend assessments of incremental increases in probabilities such as likelihood ratios, particularly for studies other than RCTs.	Thank you for your comments. A sentence to this effect has been added in the Implications for Clinical and Policy Decision Making.
TEP 8	Discussion/ Conclusion	The concept of the assessing the effect of testing on clinical and management outcomes is new and more difficult to achieve. Most prior work has looked more narrowly at test performance which is useful as a first step for new technologies but true comparative effectiveness, as the authors point out, requires larger populations and longer and more precise followup. Also, many studies were performed in the ED setting which is a different population but easier to capture and hence test. (Would add to the paragraph on p 95 about applicability: With >50% of cardiologists now integrated into hospital systems, true outpatient population studies could now more easily be attempted.)	Thank you for your comments. The section on evidence gaps and future research recommendations has been revised.

Commentator & Affiliation	Section	Comment	Response
TEP 1	Tables	In table 4, dose to an atomic bomb survivor is listed at 200 mSv. I think this figure is very misleading and would remove it. Most survivors received doses of less than 50 mSv, and thus the overall median is less than 50 mSv, but people close to the hypocenter had doses of well over 200 mSv. I would remove this line from the table. Also, PET only lists doses for FDG, which is an agent used for viability testing, not for functional testing as analyzed in this report. You should include Rb-82 and N13-ammonia in this table as well. Also, “ECHO” is not an acronym and should be listed as “Echocardiogram.”	The reference to the atomic bomb radiation has been removed, and edits have been made to the radiation exposure table and text.
Peer Reviewer 1	General	A major challenge is that the definition of "intermediate risk" is 10-90% which is a huge range. A person at 10% risk is very different than a person with 90% pretest risk.	Thank you for your comments.
Peer Reviewer 1	General	Although the majority of questions are clearly and appropriately stated, one very important question is whether or not low risk patients should even be tested at all, given the extremely likelihood of false positive tests with a low baseline risk. An important question not addressed should be the impact of one of these noninvasive tests vs no testing in those at low risk.	There were no studies identified that evaluated testing versus no testing in the population of interest; this was considered.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 2	General	This report aims to evaluate the comparative effectiveness and harms of different noninvasive testing for coronary artery disease (CAD) in a population with no known history of CAD. Testing technologies examined included functional tests (i.e. exercise electrocardiography (ECG), exercise/pharmacologic stress echocardiography, exercise/pharmacologic cardiac nuclear imaging with single photon emission computed tomography (SPECT) or positron emission tomography (PET), and pharmacologic stress magnetic resonance imaging (MRI)) and anatomical tests (i.e.coronary CT angiography (CCTA) and coronary artery calcium scoring (CACS)). Primary outcomes that capture effectiveness of the tests included all-cause mortality, myocardial infarction, additional noninvasive testing, referral for ICA, and subsequent revascularization (i.e., percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]). Primary outcomes that capture harmful aspect of the tests included complications of the testing (e.g. renal failure, allergic reactions, and adverse reactions to contrast or stress agents) and unintended consequence of the testing (e.g. radiation exposure, psychological consequences of diagnosis, incidental findings). All clinically meaningful.	Thank you for your comments
Peer Reviewer 2	General	The causal diagram is not helpful; consider revision.	Thank you for your comments.

Commentator & Affiliation	Section	Comment	Response
TEP 1	General	A number of important, long-awaited comparative effectiveness studies comparing cardiac imaging strategies have been published since November 2014, including over 20,000 patients. If this EPC report is published and does not include all these studies, it will be regarded as obsolete from the day it is published. Thankfully, you have added the PROMISE trial to the report despite its publication date of March 2015, but you have not included the 9,849-patient SCOT-HEART trial or the 400-patient Levsky et al study. I know you have worked very hard on this but believe that the report's usefulness demands that you extend the search through August 2015, even at the expense of delaying its release. I don't believe that these additional studies will change your conclusions, however their omission will weaken the impact of your conclusions and the report. These long-awaited studies include: 1. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, Cole J, Dolor RJ, Fordyce CB, Huang M, Khan MA, Kosinski AS, Krucoff MW, Malhotra V, Picard MH, Udelson JE, Velazquez EJ, Yow E, Cooper LS, Lee KL; PROMISE Investigators. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med. 2015 Apr 2;372(14):1291-300. doi: 10.1056/NEJMoa1415516. Epub 2015 Mar 14. 2. SCOT-HEART investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. Lancet. 2015 Jun 13;385(9985):2383-91. doi: 10.1016/S0140-6736(15)60291-4. Epub 2015 Mar 15. 3. Levsky JM, Spevack DM, Travin MI, Menegus MA, Huang PW, Clark ET, Kim CW, Hirschhorn E, Freeman KD, Tobin JN, Haramati LB. Coronary Computed Tomography Angiography Versus Radionuclide Myocardial Perfusion Imaging in Patients With Chest Pain Admitted to Telemetry: A Randomized Trial. Ann Intern Med. 2015 Aug 4;163(3):174-83. doi: 10.7326/M14-2948.	Douglas et al. 2015 was included in the draft report, and Levsky et al. 2015 was incorporated in the final report. Thank you. The SCOT-HEART trial, although it appears to be a well-done study, does not meet our inclusion criteria for the following reasons: 1. CCTA was not the first test performed in this population; at baseline (before randomization), 85% of patients had stress ECG and 12% had ICA. The PICOTS inclusion criteria are limited to studies where the first test (aside from resting ECG) is one of the noninvasive tests of interest. 2. It is unclear how the "baseline" diagnosis was derived. Based on #1 above, it appears to be based (at least in part) on the tests patients received prior to CCTA, and so, does not meet our inclusion criteria. 3. The intervention is not purely CCTA; the randomization was to CACS + CCTA.

Commentator & Affiliation	Section	Comment	Response
TEP 2	General	The report is well-researched, well-referenced, and quite clear in the summary of the data at hand. The target audience isn't necessarily well-defined. The problem with the data is that there just isn't a lot of outcome studies in this field and the review points out that out quite clearly. For many years, the only question asked in regards to imaging studies was accuracy against invasive angiography for the detection of CAD. Outcome studies have only been designed in the last 7-8 years which is why CTA as the newest player in the field is the most studied in this regard. This is why for many of the questions asked, the data is insufficient. The key questions asked are appropriate. The authors excluded testing in patients with known CAD. The report would have been more complete had studies in this population been included as well. In some places in the document, it is stated that emergency room patients are excluded, but many of the studies reviewed were done in the ED. The document should be reviewed carefully and mentions of exclusion of ED patients should be removed.	The intent from the beginning was to focus on those ***without*** known CAD as it was considered important to be able to evaluate testing is this population. Emergency room patients who did not have ACS were included; studies that excluded patients with ACS and/or had fewer than 20% of the enrolled population with ACS were included. After careful review, we are unable to locate any erroneous text regarding exclusion of ED patients.
TEP 3	General	See comments below. Basic issue is the need to clearly distinguish between two patient populations: those with ACS and those with chronic stable angina. This report appears to address both different patient populations but mixes them under categories of Low, Intermediate, and High Risk. This is especially important given the major difference in the effectiveness of invasive therapies (clearly beneficial in ACS but of uncertain if any benefit in ACS) which may help explain the lack of benefit of different diagnostic strategies in the latter case.	Classification of patient pre-test risk was based on how it was described in the studies. Only ED studies which either excluded patients with ACS were excluded *or* those for which ACS did not comprise >20% of study populations based on data reported in the included studies. Team clinicians agreed that with these exclusions, the population was likely at the "high" end of the intermediate range (and therefore our population of interest) versus patients who were high risk presenting with ACS.
TEP 4	General	Generally this is well put together and very comprehensive in terms of identifying and summarizing the citations with the most relevance and quality. It is not surprising, but disappointing that both the quality of evidence was low and comparative effectiveness uncertain for the various. commonly used methods for noninvasive testing for Coronary Artery Disease (CAD).	Thank you.
TEP 5	General	This was an extremely complex and audacious undertaking, and the author are to be congratulated thoroughly for their efforts and success.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP 5	General	Not having surveyed the entire literature myself for the purpose of this review, it is hard to be certain about the completeness of studies included, but at least with respect to the literature comparing coronary CTA with other imaging modalities, no important study I could think of was missing.	Thank you.
TEP 5	General	In general, the text is very densely written and difficult to digest but I guess that is just the nature of such a complex, extensive systematic review.	Thank you.
TEP 6	General	This report is well-written and tackles very timely, clinical meaningfully key questions. The target population is explicitly defined. A challenge in the report is the shift in the target population that occurs due to the results of the evidence review identifying studies that defined the target populations differently from the pre-defined key questions. Nevertheless, the report clearly makes that transition evident to the reader. The key questions are appropriate and explicitly stated. In the figure on p.11 that demonstrates the analytic framework and the key questions, there is not an explicit statement that vascular complications including stroke are included as adverse effects and harms of testing. Similarly this is not stated in the Executive Summary either (p E-8, line 51). However, vascular complications are represented in the larger table on p16 in the inclusion table.	We did abstract any information on vascular complications such as stroke; this has been added to the figure (the analytic framework). Where data were available for these outcomes, they are reflected in the Executive Summary (e.g., for CCTA vs. functional testing, periprocedural stroke data are provided) as well as the full report.
TEP 7	General	This is a remarkable piece of work for which the authors deserve heartiest congratulations. The methodology (as for nearly all AHRQ systematic reviews) is rigorous and the detailed. The report, though typically exhaustive, is clearly written and most certainly accurate. The irony, of course, is that after 4 decades of diagnostic testing for ischemic heart disease (IHD), we have remain uninformed about the value of these tests (absolute or relative) despite their widespread use, at tremendous cost, in clinical practice.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP 8	General	This is a very in-depth, thorough review of the evidence for comparative effectiveness and/or safety of noninvasive testing for the diagnosis of coronary artery disease and in the specific population of symptomatic patients without known CAD. This is very well written, clear and precise; it extends the current body of literature in the field by rigorously defined assessment and attempts at comparative effectiveness. This is a crucial question both clinically and for health care policy. Unfortunately, the variable quality and volume of available literature does limit the conclusions, but does serve as a call to action for target research to answer these knowledge gaps and also for better trial design.	Thank you for your comments.
Patricia Pellikka, MD, Mayo Clinic, Rochester, MN	General	On page 5 48and in the table on page 7 50 the document states that SPECT is the preferred test in LBBB. What is the evidence to support this claim In a couple small studies stress echo was superior to SPECT in patients with LBBB. Are there any studies to substantiate the authors claim that SPECT should be used	Preference for SPECT in those with LBBB may vary across settings depending on availability and local expertise. We have removed references to this.
Vinay Malhotra, MD, Society of Cardiovascular Computed Tomography, Government Relations and Advocacy	General	The Society of Cardiovascular Computed Tomography (SCCT) appreciates the opportunity to comment on the AHRQ Draft Report: *Noninvasive Testing for Coronary Artery Disease*. SCCT is the international professional society representing physicians, scientists and technologists advocating for research, education and clinical excellence in the use of cardiovascular computed tomography	Thank you for your comments.
Vinay Malhotra, MD, Society of Cardiovascular Computed Tomography, Government Relations and Advocacy	General	The accurate and early diagnosis of coronary disease is helpful in that it allows both physicians and patients to make informed decisions regarding treatment plans and prognosis of their condition. Functional testing (e.g. stress testing, spect-thallium, echo-stress) are all reasonable but have significant limitations in that their sensitivity and specificity (even when utilized in appropriate groups) are in the 80-85% range.	Thank you.
Vinay Malhotra, MD, Society of Cardiovascular Computed Tomography, Government Relations and Advocacy	General	Invasive coronary angiography is the gold standard by which all other testing is gauged and is nearly 100% accurate in detecting coronary disease. It is quite good (along with adjunctive functional invasive testing) in determining which blockages require treatment. However, this is a costly procedure and while overall low risk, there are potentially life threatening consequences associated with invasive testing of this kind.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Vinay Malhotra, MD, Society of Cardiovascular Computed Tomography, Government Relations and Advocacy	General	Coronary CTA allows for anatomic evaluation of the coronary tree which is nearly 100% specific. Coronary CTA can rule out coronary disease in patients, with extremely high negative predictive value for hard events (e.g. myocardial infarction) up to nearly seven years. In addition, coronary CTA is better than any other modality in screening for sub clinical plaque (both calcified and soft) in asymptomatic patients.	Thank you.
Vinay Malhotra, MD, Society of Cardiovascular Computed Tomography, Government Relations and Advocacy	General	For patients at low risk, no testing is usually needed (of any kind). However, in patients who are low-tomoderate risk, or patients who have symptoms (even atypical symptoms) there is a need for a safe, effective, discriminator between patients who have no disease and patients who have *some* coronary disease. This leads to definitive treatment and management strategies (e.g. initiation of statins, aggressive blood pressure control, and sometimes invasive evaluation). Coronary CTA is an excellent modality to reduce utilization of cardiac catheterization in patients with symptoms who are found *not* to have coronary disease, without the need for costly or invasive testing.	Thank you.
Vinay Malhotra, MD, Society of Cardiovascular Computed Tomography, Government Relations and Advocacy	General	Use of coronary CTA is potentially cost saving and has a definite impact on a range of issues such as medical compliance (e.g. calcium scoring) and downstream testing. It is a safe test, as the radiation dose with current scanners is nearly 100x less than the threshold for “low dose” radiation, and as there is no invasive component, the only potential issue for acute problems relates to contrast reactions.	Thank you.
Vinay Malhotra, MD, Society of Cardiovascular Computed Tomography, Government Relations and Advocacy	General	Attached to this comment is a list of key references in the field of coronary CTA. Thank you for your consideration of these comments.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Vinay Malhotra, MD, Society of Cardiovascular Computed Tomography, Government Relations and Advocacy	General	**Key References CCTA Initial Validation** (1) Moshage EW, Achenbach S, Seese B, Bachmann K, Kirchgeorg M. Radiology 1995;196:707-714. (2) Achenbach S, Giesler T, Ropers D, et al. Detection of coronary artery stenoses by contrastenhanced, retrospectively electrocardiographically-gated, multislice spiral computed tomography. Circulation. 2001; 103: 2535–2538. (3) Nieman K, Cademartiri F, Lemos PA, Raaijmakers R, Pattynama PMT, and Feyter PJ. Reliable Noninvasive Coronary Angiography With Fast Submillimeter Multislice Spiral Computed Tomography. Circulation. 2002;106:2051-2054. (4) Ropers D, Baum U, Pohle K, Anders K, Ulzheumer S, Ohnesorge B, Schlundt C, Bautz W, Daniel WG, Achenbach S. Detection of coronary artery stenosis with thin-slice multi-detector row spiral computed tomography and multiplanar reconstruction. Circulation 2003;107:664-666. (5) Leber AW, Knez A, von Ziegler F, Becker A, Nikolaou K, Paul S, Wintersperger, B, Reiser M, Becker CR, Steinbeck G, Boekstegers P. Quantification of obstructive and nonobstructive coronary lesions by 64-slice computed tomography: a comparative study with quantitative coronary angiography and intravascular ultrasound. J Am Coll Cardiol. 2005 Jul 5;46(1):147-54. (6) Leschka S, Alkadhi H, Plass A, Desbiolles L, Grünenfelder J, Marincek B, Wildermuth S. Accuracy of MSCT coronary angiography with 64-slice technology:first experience. Eur Heart J. 2005 Aug;26(15):1482-7.	The primary focus of this report is to determine whether noninvasive tests improve clinical health outcomes and impact patient management. Information on the traditional test parameters of diagnostic accuracy are described in the background section for contextual purposes only and were not examined via the formal systematic review process. We reviewed the suggested references and they did not meet the systematic review inclusion criteria.

Commentator & Affiliation	Section	Comment	Response
Vinay Malhotra, MD, Society of Cardiovascular Computed Tomography, Government Relations and Advocacy	General	**Key References CCTA Multi-Center trials – Diagnostic Accuracy vs Invasive coronary Angiography** **(**7) Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, Scherer M, Bellinger R, Martin A, Benton R, Delago A, Min JK. Diagnostic performance of 64 multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. J Am Coll Cardiol. 2008 Nov 18;52(21):1724-32. (8) Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, Paul N, Clouse ME, Shapiro EP, Hoe J, Lardo AC, Bush DE, de Roos A, Cox C, Brinker J, Lima JA. Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med. 2008 Nov 27;359(22):2324-36. (9) Meijboom WB, Meijs MF, Schuijf JD, Cramer MJ, Mollet NR, van Mieghem CA, Nieman K, van Werkhoven JM, Pundziute G, Weustink AC, de Vos AM, Pugliese F, Rensing B, Jukema JW, Bax JJ, Prokop M, Doevendans PA, Hunink MG, Krestin GP, de Feyter PJ. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. J Am Coll Cardiol. 2008 Dec 16;52(25):2135-44.	The primary focus of this report is to determine whether noninvasive tests improve clinical health outcomes and impact patient management. Information on the traditional test parameters of diagnostic accuracy are described in the background section for contextual purposes only and were not examined via the formal systematic review proce ess. The suggested references did not meet the systematic review inclusion criteria.
Vinay Malhotra, MD, Society of Cardiovascular Computed Tomography, Government Relations and Advocacy	General	**Key References CCTA Metanalysis – Diagnostic Accuracy vs Invasive coronary Angiography** (10) Mowatt G, Cook JA, Hillis GS, Walker S, Fraser C, Jia X, Waugh N. 64-Slice computed tomography angiography in the diagnosis and assessment of coronary artery disease: systematic review and meta-analysis. Heart. 2008 Nov;94(11):1386-93. (11) Vanhoenacker PK, Heijenbrok-Kal MH, Van Heste R, Decramer I, Van Hoe LR, Wijns W, Hunink MG. Diagnostic performance of multidetector CT angiography for assessment of coronary artery disease: meta-analysis. Radiology. 2007 Aug;244(2):419-28.	The primary focus of this report is to determine whether noninvasive tests improve clinical health outcomes and impact patient management. Information on the traditional test parameters of diagnostic accuracy are described in the background section for contextual purposes only and were not examined via the formal systematic review process. The suggested references did not meet the systematic review inclusion criteria.

Commentator & Affiliation	Section	Comment	Response
Vinay Malhotra, MD, Society of Cardiovascular Computed Tomography, Government Relations and Advocacy	General	**Key References CCTA Radiation Dose** (12) Einstein AJ, Henzlova MJ, Rajagopalan S. Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. JAMA. 2007 Jul 18;298(3):317-23. (13) Raff GL, Chinnaiyan KM, Share DA, Goraya TY, Kazerooni EA, Moscucci M, Gentry RE, Abidov A; Advanced Cardiovascular Imaging Consortium Co-Investigators. Radiation dose from cardiac computed tomography before and after implementation of radiation dose-reduction techniques. JAMA. 2009 Jun 10;301(22):2340-8. (14) Halliburton SS, Abbara S, Chen MY, Gentry R, Mahesh M, Raff GL, Shaw LJ, Hausleiter J; Society of Cardiovascular Computed Tomography. SCCT guidelines on radiation dose and doseoptimization strategies in cardiovascular CT. J Cardiovasc Comput Tomogr. 2011 Jul- Aug;5(4):198-224. (15) Earls JP, Berman EL, Urban BA, Curry CA, Lane JL, Jennings RS, McCulloch CC, Hsieh J, Londt JH. Prospectively gated transverse coronary CT angiography versus retrospectively gated helical technique: improved image quality and reduced radiation dose. Radiology. 2008 Mar;246(3):742-53. (16) Chinnaiyan KM, Boura JA, DePetris A, Gentry R, Abidov A, Share DA, Raff GL; Advanced Cardiovascular Imaging Consortium Coinvestigators. Progressive radiation dose reduction from coronary computed tomography angiography in a statewide collaborative quality improvement program: results from the Advanced Cardiovascular Imaging Consortium. Circ Cardiovasc Imaging. 2013 Sep;6(5):646-54.	Information on radiation safety is provided for context. Where appropriate, information from the suggested references was incorporated into the background section of the report. For example, Halliburton et al. 2011 (14) is included in the current draft report in the background section on radiation. The studies do not meet our formal inclusion criteria for the systematic review portion to answer the key questions (exclusion reasons notted below); however, relevant information from these papers has been incorporated in the contextual section. (12) Einstein et al. 2007 (phantom simulation models, does not address systematic review questions) (13, 16) Raff et al. 2009 and Chinnaiyan et al 2013 (evaluating a radiation dose reduction program) (15) Earls et al. 2008 (wrong comparison; pro-spective vs. retrospective gating; does not address systematic review questions)

Commentator & Affiliation	Section	Comment	Response
Vinay Malhotra, MD, Society of Cardiovascular Computed Tomography, Government Relations and Advocacy	General	**Key References CCTA in the Emergency Department – Large Randomized Multi-Center trials** (17) Goldstein JA, Chinnaiyan KM, Abidov A, Achenbach S, Berman DS, Hayes SW, Hoffmann U, Lesser JR, Mikati IA, O'Neil BJ, Shaw LJ, Shen MY, Valeti US, Raff GL. The CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) trial. J Am Coll Cardiol 2011; 58:1414-22. (18) Litt HI, Gatsonis C, Snyder B, Singh H, Miller CD, Entrikin DW, Leaming JM, Gavin LJ, Pacella CB, Hollander JE. CT angiography for safe discharge of patients with possible acute coronary syndromes. N Engl J Med 2012; 366:1393-403. (19) Hoffmann U, Truong QA, Schoenfeld DA, Chou ET, Woodard PK, Nagurney JT, Pope JH, Hauser TH, White CS, Weiner SG, Kalanjian S, Mullins ME, Mikati I, Peacock WF, Zakroysky P, Hayden D, Goehler A, Lee H, Gazelle GS, Wiviott SD, Fleg JL, Udelson JE. Coronary CT angiography versus standard evaluation in acute chest pain. N Engl J Med 2012; 367:299-308. (20) Hamilton-Craig C, Fifoot A, Hansen M, Pincus M, Chan J, Walters DL, Branch KR. Diagnostic performance and cost of CT angiography versus stress ECG--a randomized prospective study of suspected acute coronary syndrome chest pain in the emergency department (CT-COMPARE). Int J Cardiol. 2014 Dec 20;177(3):867-73.	All four trials were included report.

Commentator & Affiliation	Section	Comment	Response
Vinay Malhotra, MD, Society of Cardiovascular Computed Tomography, Government Relations and Advocacy	General	**Key References CCTA in the Emergency Department – Implementation in Clinical Practice** (21) Poon M, Cortegiano M, Abramowicz AJ, et al. Associations between routine coronary computed tomographic angiography and reduced unnecessary hospital admissions, length of stay, recidivism rates, and invasive coronary angiography in the emergency department triage of chest pain. J Am Coll Cardiol. 2013;62(6):543e552. (22) Cury RC, Feuchtner G, Battle J, et al. Triage of Patients Presenting with Chest Pain to the Emergency Department: Implementation of Coronary CTA in a Large Urban Hospital Healthcare System. Am J Roentgenol. 2013;200(1):57e65. (23) Cury RC, Feuchtner G, Mascioli C, et al. Cardiac CT in the emergency department: convincing evidence, but cautious implementation. J Nucl Cardiol. 2011 Apr;18(2):331-41. (24) Raff GL, Chinnaiyan KM, Cury RC, et al. SCCT guidelines on the use of coronary computed tomographic angiography for patients presenting with acute chest pain to the emergency department: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. J Cardiovasc Comput Tomogr. 2014;8(4): 254e271. (25) Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-STElevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;64(24):e139ee228. (26) Maroules CD, Blaha MJ, El-Haddad MA, Ferencik M, Cury RC. Establishing a successful coronary CT angiography program in the emergency department: official writing of the Fellow and Resident Leaders of the Society of Cardiovascular Computed Tomography (FiRST). J Cardiovasc Comput Tomogr. 2013;7(3):150e156.	Amsterdam et al. 2014 (25) is included in the background section of the current draft report. The observational study by Poon (21) has been added. The following studies do not meet our inclusion criteria (reason stated): (22) Cury et al. 2013 (no comparison test; evaluating a chest pain triage protocol using CCTA) (23) Cury et al. 2011 (wrong study design; narrative review) (24) Raff et al. 2014: (CCTA use guideline; no comparison/discussion of other testing modalities; does not describe outcomes of interest; pertinent references are included in the report) (26) Maroules et al. 2013 (wrong study design; narrative review)
Vinay Malhotra, MD, Society of Cardiovascular Computed Tomography, Government	General	**Key References Coronary CTA as a Gatekeeper to the Cath Lab** (27) Chinnaiyan KM, Raff GL, Goraya T, et al. Coronary computed tomography angiography after stress testing: results from a multicenter, statewide registry, ACIC	None of these studies met our inclusion criteria (reason stated): (27) Chinnaiyan et al. 2012 (wrong intervention; CCTA not first test--all patients had CCTA within 3 months of a

Commentator & Affiliation	Section	Comment	Response
Relations and Advocacy		(Advanced Cardiovascular Imaging Consortium). J Am Coll Cardiol. 2012;59:688e695. (28) Shaw LJ, Hausleiter J, Achenbach S, et al, CONFIRM Registry Investigators. Coronary computed tomographic angiography as a gatekeeper to invasive diagnostic and surgical procedures: results from the multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: an International Multicenter) registry. J Am Coll Cardiol. 2012;60(20):2103e2114. (29) Patel MR, Dai D, Hernandez AF, Douglas PS, et al. Prevalence and predictors of nonobstructive coronary artery disease identified with coronary angiography in contemporary clinical practice. Am Heart J. 2014;167(6):846e852.e2. (30) Cury RC. President's page: coronary CT angiography as a gatekeeper to the catheterization laboratory. J Cardiovasc Comput Tomogr. 2014 Nov-Dec;8(6):480-2.	stress test) (28) Shaw et al. 2012 (no comparator, CCTA only) (29) Patel et al. 2014 (outcome not part of review scope: correlation between test results and likelihood of nonobstructive CAD in patients undergoing elective ICA--no hard, clinical outcomes reported) (30) Cury et al. 2014 (wrong publication type; editorial/review)
Vinay Malhotra, MD, Society of Cardiovascular Computed Tomography, Government Relations and Advocacy	General	**Key References CCTA in the Symptomatic Stable Chest Pain – Large Randomized Multi-Center Trials** (31) Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, Cole J, Dolor RJ, Fordyce CB, Huang M, Khan MA, Kosinski AS, Krucoff MW, Malhotra V, Picard MH, Udelson JE, Velazquez EJ, Yow E, Cooper LS, Lee KL; PROMISE Investigators. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med. 2015 Apr 2;372(14):1291-300. (32) SCOT-HEART investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. Lancet. 2015 Mar 13. pii: S0140-6736(15)60291-4.	Douglas et al. 2015 (31) was included in the draft report. The SCOT-HEART trial (32), although it appears to be a well done study, does not meet our inclusion criteria for the following reasons: 1. CCTA was not the first test performed in this population; at baseline (before randomization), 85% of patients had stress ECG and 12% had ICA. The PICOTS criteria limits inclusion to studies in which the first test (aside from resting ECG) is one of the noninvasive tests of interest. 2. It is unclear how the "baseline" diagnosis was derived. Based on #1 above, it appears to be based (at least in part) on the tests patients received prior to CCTA, and so, does not meet our inclusion criteria. 3. The intervention is not purely CCTA; the randomization was to CACS + CCTA.

Commentator & Affiliation	Section	Comment	Response
Vinay Malhotra, MD, Society of Cardiovascular Computed Tomography, Government Relations and Advocacy	General	**Key References Stress Myocardial CT Perfusion – Multi-Center Trials Validation against SPECT and Invasive coronary Angiography** (33) Rochitte CE, George RT, Chen MY, et al. Computed tomography angiography and perfusion to assess coronary artery stenosis causing perfusion defects by single photon emission computed tomography: the CORE320 study. Eur Heart J. 2014 May;35(17):1120-30. (34) Cury RC, Kitt TM, Feaheny K, Blankstein R, Ghoshhajra BB, Budoff MJ, Leipsic J, Min JK, Akin J, George RT. A randomized, multicenter, multivendor study of myocardial perfusion imaging with regadenoson CT perfusion vs single photon emission CT. J Cardiovasc Comput Tomogr. 2015 Mar-Apr;9(2):103-12.	Per the PICOTS criteria, CT perfusion is excluded.
Vinay Malhotra, MD, Society of Cardiovascular Computed Tomography, Government Relations and Advocacy	General	**Key References FFR-CT – Multi-Center Trials Validation against Invasive FFR and Invasive coronary Angiography** (35) Nørgaard BL, Leipsic J, Gaur S, et al; NXT Trial Study Group. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). J Am Coll Cardiol. 2014 Apr 1;63(12):1145-55. (36) Min JK, Leipsic J, Pencina MJ, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. JAMA. 2012 Sep 26;308(12):1237-45.	Per the PICOTS criteria, CT-based FFR is excluded.
Peer Reviewer 1	Clarity and Usability	Yes it is clear and usable. the major conclusions are clear. They have clearly defined the main limitations of the available evidence.	Thank you.
Peer Reviewer 1	Clarity and Usability	As described above, if the two additional questions (testing vs no testing in low risk AND do results differ in ED vs outpatient settings) could be addressed the report would be strengthened and more clinically useful.	Some additional clarification regarding ED and outpatients has been added throughout. No studies comparing testing vs. no testing were identified.
Peer Reviewer 2	Clarity and Usability	This is reasonably well structured and organized.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP 2	Clarity and Usability	I was confused by the executive summary which seemed to me to be half the length of the full document. To be truly useful, the summary should be significantly shorter than the full document. In many places, the text and tables are duplicative. That being said, there are readers who prefer one over the other, so it may not make sense to remove one. This is the first document that I am aware of that attempts to synthesize all of the outcome data in regards to noninvasive cardiac testing and in that regard should be useful to the intended audience. In addition, the recommendations for future research are quite useful in shaping the field for years to come.	Thank you.
TEP 3	Clarity and Usability	OK	Thank you.
TEP 4	Clarity and Usability	Yes to the first two questions. The conclusions are relevant but do not clarify how best solve the problems of the uncertainties discovered in the report. See comment above in (e) relevant to the last question.	Thank you for your comments; Edits to the discussion of research gaps and future research have been made.
TEP 4	Clarity and Usability	Additionally, with the advent of a variety of initiatives targeting the reduction of "low value" health care services, some additional insights should be discussed relative to the costs of these different strategies commonly used in practice. There certainly must be existing additional information on the comparative economics of these methods.	Thank you for your comments. Description and discussion of costs, value and/or cost-effectiveness were not part of the scope of this report.
TEP 4	Clarity and Usability	I am also wondering if those organizations (such as ACC and AHA) would actively participate in a more cautious look at existing guidelines and appropriate use criteria given the findings of this evaluation.	Thank you.
TEP 5	Clarity and Usability	The report is well structured and organized, and the main points are clearly presented.	Thank you.
TEP 5	Clarity and Usability	The conclusions the authors were able to draw were limited due to limitations of the data they were able to work with (and their appropriately stringent inclusion and exclusion criteria), hence new information and understanding is limited to the clear, concise and comprehensive analytic summary of the available evidence on this topic.	Thank you.
TEP 5	Clarity and Usability	The key points that the authors were able to make, in particular relating to future directions, are very clearly made.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP 6	Clarity and Usability	The report is well structured and organized. There is a lot of detail in the report and the fact that it is a comparison report with sub-sets of inclusion focus makes it particularly challenging to organize. My major comment on organization relates to perhaps adding a table that lays out the template for what is to come and how the results will be presented. Once one understands the structure and format of the results that are forthcoming, it is easier to read through. The conclusions are relevant to practice, and to some extent to areas where guidelines may be informed. The most important relevance seems to be where further research is needed particularly related to post-test probability and clinical outcomes.	We have added a table that outlines the tests compared.
TEP 7	Clarity and Usability	To reiterate, this is a superb piece of but its sheer bulk limits the degree to which it can be applied. A very simple summary of findings would be welcome.	Thank you for your comments.
TEP 8	Clarity and Usability	See General comments.	Thank you.